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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/808,382	REUBINOFF ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-46,51,56-58,60-68,86 and 88-99* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-46,51,56-58,60-68,86 and 88-99* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/25/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Response and Amendment, filed 8/25/05, has been entered. Claims 39-45, 51, 56, 60, 63-65, 88-90, 92, 95 are amended; claim 87 is cancelled; claims 96-99 are newly added; claims 39-46, 51, 56-58, 60-68, 86, 88-99 are pending and under current examination.

Information Disclosure Statement

Applicants' Information Disclosure Statement, filed 8/25/05 has been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-46, 51, 56-58, 60-68, 86, 88-99 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection. This rejection is maintained for reasons of record advanced in the prior Office action, mailed 2/23/05.

Applicants argue that the neural progenitor cells (NPCs) have now been amended to state that they are, "capable of further differentiation to a cell selected from the group consisting of neurons, oligodendrocytes and astrocytes" and show that Applicants have possession of the claimed invention by citing various portions of the specification as evidence. See p. 11 of the Response.

These arguments are considered, but not persuasive. The identification and generation of the NPCs, which are produced by inducing somatic differentiation of human pluripotent ES cells are found to lack an adequate written description. Applicants state that the specification clearly discloses the preparation of NPCs from hES cells, as well as the differentiation of the NPCs to an intermediate cell type, to somatic cells, such as neurons, oligodendrocytes and astrocytes. Applicants point to the page 22, lines 29 to page 23, lines 1-2; page 39 to 42, pages 64-66 and page 76 (Example 5). Page 22-23 teaches a neural progenitor cell that is identified by any particular markers (NCAM, nestin, vimentin, Pax-6, and the lack of expression of Oct-4), page 39-42 each how to produce NPCs from hES cells, using serum free medium, the general production of the PGCs, and the identification of the PGCs from various markers (listed above), pages 64-66 teach derivation of NPCs, and the identification of cells by the expression of the above-mentioned markers, and the propogation of these cells (see Example 5). Applicants point to various figures (7, 9, 11-13, 21-28). These figures provide the same information as the specification – that the cells produced by the claimed method express particular marker(s) (NCAM, nestin and vimentin). However, this does not provide any description for the NPCs, as stated in the prior Office action, that these markers are found in other cell types. See also, pages 3-4 of the prior rejection, mailed 2/23/05. In short, the prior Office action provided sufficient evidence to show that NCAM is expressed in early embryonic development, in the derivative of all three germ layers, and after birth is restricted to neural tissues; Pax-6 is important in the development of the eye; nestin is expressed in islet cells (see Cremer, Baumer & Wang, cited previously). The identification of NPCs by a particular marker, as taught by the instant specification, fails to adequately describe a NPC. Althought he cells that Applicants have taught express some combination of these markers, this does not indicated that they are NPCs, as these markers are expressed in cell

types other than NPCs, as evidenced above. Although NPCs may also express these markers, they are not exclusive to NPCs.

Applicants argue that transplantation data described in the specification show that intermediate NPCs differentiated to further somatic cells after transplantation (figures 21-23, 29 and 30). These arguments are not persuasive. These figures fail to provide description for the NPCs; these figures are directed to the transplantation of the NPCs into lateral cerebral ventricles of newborn rats and mice. The figures show analysis of the migration of the human cells, and the expression of markers (GFAP for astrocytes, CNPase for oligodendrocytes). Although this shows that the NPCs are capable of differentiation to various neural cell types, this fails to provide sufficient guidance for the NPCs, which are essential to practicing the claimed method. The specification teaches how to identify NPCs based upon expression (or lack thereof) of particular markers. However, the markers that are contemplated by the specification are not unique to NPCs, thus, the NPCs which are used in the claimed methods lack a written description because the specification fails to provide relevant identifying characteristics of these cells.

Claims 39-46, 51, 56-58, 60-68, 86, 88-99 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for reasons of record advanced in the prior Office action, mailed 2/23/05.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors

have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants' Arguments. Applicants argue that the Verfaillie *et al.*, cited in the prior Office action, is directed to the difficulties in attempting to derive a particular cell type from mouse embryoid bodies, which are formed by spontaneous differentiation of mouse ES cells, and that in the instant case, the NPCs are derived from human ES cells, under controlled differentiation conditions, for example, the use of serum-free media, which results in spheres that contain NPCs. Further, Applicants argue that the claims have now been amended to specifically delineate that NPCs are differentiated from hES cells and are capable of further differentiation to cells such as neurons, oligodendrocytes, and astrocytes, and in specific embodiments, the NPCs are characterized by specific expression markers. Applicants argue that the claims are enabled because the specification teaches how to prepare NPCs from hES cells, and to further differentiate the NPCs into desired somatic cells. Thus, Applicants argue that given these teachings, one of skill in the art could make NPCs from hES cells, and readily determine whether an intermediate cell type generated by the following method steps is an NPC, for by example, culturing the cell and inducing differentiation, as disclosed by the specification. Thus, the intermediate cell would be determined to be an NPC if the resultant cells are neurons, oligodendrocytes, and/or astrocytes. See pp. 12-13 of the Response.

These arguments have been considered but are not persuasive. The claimed invention is to the directed differentiation of ES cells to a particular cell type, in the instant case, cells of neuronal lineage. Verfaillie provides guidance with regard to the unpredictability found in this art. On a preliminary note, the Examiner notes that Verfaillie *et al.* is directed to human ES cells, particularly they state that the proposed application of human ES cells could potentially be treated with inducing agents to convert them into a particular cell type of interest, but this has not proven

possible even in the mouse system. They further teach that although it is possible to produce differentiated cells from human ES cells, it is not clear, for example, if neural progenitors, isolated by these means show properties distinct from neural stem cells isolated from embryonic, fetal, or adult sources (see p. 379, col. 2). The breadth of the claims are directed to a "controlled differentiating condition" however, the art clearly shows that it would require undue experimentation for one of skill in the art to determine with a controlled differentiating condition is, and then use this condition to produce particular cell types (in the instant case, neural progenitor cells). Furthermore, it is noted that the progression of undifferentiated cells to committed cells, such as neural cells, occurs on a continuum. Thus, the instant specification teaches that the NPCs can be identified by particular markers. The Examiner has already established that the art recognizes that these markers are expressed by cells other than NPCs, and thus, one of skill in the art, given the teachings of the specification, the state of the art, would have to practice undue experimentation to make and use the NPCs which are produced upon differentiation of hES cells, as one would not know if the NPCs were true neural progenitor cells, or another cell type that merely expresses the same markers.

Accordingly, in view of the unpredictable state of the art of directed differentiation, the lack of teaching or guidance provided by the specification with regard to the generation of neural progenitor cells, the art which teaches that the previously recited markers are found in cell types other than neural progenitor cells, it would have required undue experimentation for one of skill in the art to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

Claims 39-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Shamblott *et al.* (cited in the Office action mailed 7/29/04). This a new grounds of rejection necessitated by Applicants' Amendments to the claims.

Applicants have amended the claims such that particular markers are not used to identify the human neural progenitor cells. The claims are directed to methods of inducing somatic differentiation of human ES cells *in vitro* into human NPCs, wherein the NPCs are capable of further differentiation to a cell selected from the group consisting of neurons, oligodendrocytes, and an astorcyte, by obtaining an undifferentiated hES cell, and culturing the hES cells under a controlled differentiating condition which is non-permissive for stem cell renewl, does not kill cells or induce unidirectional differentiation toward extra embryonic lineages to induce somatic differentiation of the hES cells.

Claims 44 and 45 recite undifferentiated ES cells prepared by a specific method. Thus, the ES cells are product by process claims. Note that with regard to claims 40 and 41, which discuss the expression of various undifferentiated ES cell markers, these markers are inherent properties of undifferentiated ES cells. That is, "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Shamblott teach the generation of pluripotent human ES cells from cultured human primordial germ cells. Gonadal ridges from post-fertilization human embryos were collected and the cells cultured. The cells were analyzed by detection of AP activity and immunohistochemistry. See Methods & Materials. The cells were found to be positive for five immunological markers of ES cells (SSEA-1, SSEA-2, SSEA-4, TRA-1-60, TRA-1-81), see Abstract. The immunohistochemical

analysis of embryoid bodies revealed a wide variety of differentiated cell types, including derivatives of all three embryonic germ layers (see Abstract). Particularly, the immunohistochemical analysis of the embryoid bodies found ectodermal derivatives of cells suggestive of neuroepithelial and antineurofilament cells. See p. 13729, 2nd column, 1st full ¶. Shamblott teaches that the cells are pluripotent stem cells, that are positive for markers commonly used to identify pluripotent stem cells, have morphology similar to mouse ES and EG cells and maintain a normal and stable karyotype, and can be differentiated into a wide variety of cell types.

As stated in prior Office actions, the specification does not provide a definition of "controlled differentiating condition" and thus, the broadest reasonable interpretation hte claim has been given to the term. The differentiation observed by Shamblott is clearly "controlled" in that the cells develop into all three embryonicgerm layers. Tehre is no stem cell renewal once the germ layers are formed, and there is no taught unidirectional differentiation towards extraemryonic lineages. Thus, the characteristics of controlled differentiation, as defined by the claim, are met by Shamblott. Accordingly, Shamblott anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinar
> y skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the

inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 51, 95 and newly added claim 99 under 35 U.S.C. 103(a) as being obvious over Thomson in view of Brustle, is maintained for reasons of record advanced in the prior Office actions, mailed 2/23/05 and 7/29/04.

Thomson teach embryonic stem cell lines derived from human blastocysts. They teach that the cells are isolated from human embryos which were cultured to blastocyst stage and the inner cell masses isolated and cultured (see p. 1145, 2nd column). They teach that the cells expressed markers for human pluritpoent stem cells (p. 1145, col. 3, last paragraph), they teach that the cells had a normal karyotype (p. 1145, 2nd column) and produced teratomas when injected into SCID mice (p. 1146, 1st column). Brustle teach methods of inducing differentiation of mouse ES cells to glial precursors, a somatic progenitor cell, by culturing mouse ES cells in the presence of FGF2 and PDGF-AA in DMEM/F12 media and on polyornithine coated dishes (p. 754, 2nd col. 2, lines 1-7; p. 756, 1st col., lines 14-27). The withdrawn of growth factors caused the progenitor/stem cells to differentiate into oligodendrocytes (p. 754, 2nd col., lines 13-15, p. 756, col. 1, lines 30-31).

In the prior rejection, the Examiner stated that although culture conditions for maintaining mouse and human ES cells are different, this does not translate to different conditions when inducing differentiation of ES cells. The Examiner cited Mizuseki *et al.*, a post-filing art, which provides evidence to show under the same conditions, mouse and human ES cells could be induced to differentiate into neural cells. Thus, it would be obvious to combine the teachings of Thomsom and Brustle, as Thomson teaches human ES cells, and Brustle teaches conditions to culture ES

Thomson teaches human ES cells, and Brustle teaches conditions to culture ES cells to produce neural cells. They teach the resultant cells have the morphology of oligodendrocytes and express the oligodendroglial antigen, O4. See Figure 1.

Applicants argue that is improper to rely upon Mizuseki as evidence of requiste motivation and/or reasonable expectation of success. Applicants further argue that although both mouse and human ES cell produced neurons, only mouse ES cells produced cells expressing dorsal and ventral neural markers, whereas primate ES cells did not differentiate as efficiently as mouse ES cells, and only produced cells with neural markers. See p. 15 of the Response.

These arguments are not persuasive. The Examiner cited Mizuseki in response to Applicants' prior arguments, and this reference is not relied upon for motivation or reasonable expectation of success, and this reference is not relied upon for this rejection. Furthermore, Applicants' arguments, regarding the cell expression markers, or efficiency of differentiation are not within the scope of this rejection. The claims do not require a particular yield, or expression of dorsal and ventral neural markers. The claims merely require that upon differentiation of human ES cells, in a controlling differentiation condition, the production of human neural progenitor cells would result.

Applicants provide Xu *et al.*, (2002, Exhibit B) (which, the Examiner notes, is also post-filing art) to show that using BMP-4, there fundamental differences between human and mouse ES cells, which differentiate poorly to trophoblast cells. Applicants also provide Xu (2002, Exhibit C) which teaches that hES cell cardiomyocyte differentiation is indeed quite different from mouse ES or mouse EC cells, in that DMSO and RA enhance mEC/mES cell cardiogenesis and do not show this effect in hES cell differentiation. See p. 15 of the Response.

These references have been considered, but are not persuasive. Xu (Exhibit B) teaches that mouse ES cells yield very low trophoblast cells. This article cites Beddington *et al.* (**Development**, 105:733-737 (1989)), as evidence for this,

Beddington *et al.* teaches that injection of ES cells into host blastocysts, and the testing of their developmental potential in the developing embryo. This is not within the scope of the instant rejection, as this article is directed to *in vivo* differentiation. The instant claims are directed to *in vitro* culturing of ES cells to produce neural cells under broad conditions. There is no comparison between culturing mouse ES cells in the same conditions as human ES cells, and comparison of resultant cells. Xu (Exhibit C) is directed to enhancing cardiogenesis. The claims merely require the induction of the hES cells to a particular cell type, and not to a particular yield of cells. Both cells from a human and mouse are capable of cardiomyocyte differentiation, and although Xu teaches enhancement of cardiogenesis in mouse ES cells, there is no evidence provided by Xu that the conditions used in mouse cells would not work in human cells, for the production of cardiomyocytes.

Applicants argue that Thomsom teaches that there are differences between early mouse and human development, as indicated by the markers in ES and EC cells in the two species, and that Thomson thus suggests that citations relating the two species should not be combined. There is no teaching in Thomson that suggested that citations relating to the two (mouse and human) species cannot or should not be combined. They merely show the differences between surface markers of undifferentiated mouse and human ES cells. Applicants argue that Thomson only teaches that ES cells have the ability to form derivatives of all three embryonic germ layers, and there is no appreciation of any intermediate cell type, much less an NPC cell. Thomson teaches that hES cells can differentiate in many different cell types as part of a teratoma and that teratoma formation only reflects intrinsic differentiation abilities of ES cells in the context of a unique *in vivo* environment, and that these teachings do not suggest by any means as to how an intermediate cell type can be obtained from hES cells *in vitro*. Thus, if one of skill in the art were to follow the teachings of Thomson, those skilled in the art would

not have focuses on obtaining any intermediate cell types, as the cell s differentiated from hES cells, taught by Thomson, were somatic cells.

One of ordinary skill in the art would recognize that mouse and human have different requirements for maintaining an undifferentiated state, but it is maintained that it would have been obvious for one of skill, given the human ES cells of Thomson, to culture the cells under the conditions, taught by Brustle, to arrive at the claimed invention, with a reasonable expectation of success. Furthermore, it is noted that Thomson provides support for human ES cells, which are capable of differentiating into various cell types, including neural cells. Teratoma formation is routinely used in the art to show the differentiation potential of a cell, in the instant case, an ES cell. Thomson is not relied upon to produce the NPCs, as Brustle provides the necessary method steps and conditions to produce neural progenitor cells. Furthermore, it is noted that the NPCs, as contemplated by Applicants, are also somatic cells. Although they may be less differentiated than terminally differentiated cells in that the instantly contemplated NPCs have the capability to differentiate into various neural cell types, they remain somatic cells.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

The prior rejection of claims 56-58 and 86 under 35 U.S.C. 103(a) as being unpatentable over Thomson et al. in view of Brustle et al. and Stemple et al. is maintained for reasons of record advanced in the prior Office actions, mailed 2/23/05 and 7/29/04.

Applicants present the same arguments as above, with regard to the combination of Thomson and Brustle, and reassert that those of skill in the art would not have been motivated to combine the teachings of Thomson and Brustle with Stemple. Applicants argue that Stemple is directed to neural crest cells, which cannot be properly applied to NPCs, as presently claimed. See p. 17 of the Response.

This is not found to be persuasive. First, the claims require that the neural progenitor cells are derived from human ES cells. Thus, a neural crest cell is originally derived from an ES cell. Further, it is maintained that Stemple's teachings provide sufficient motivation to reach the claimed invention because they teach the requirement of poly-D lysine, and the growth of neural stem cells in the presence retinoic acid. Thus, it is maintained that, at the time of the instant invention, it would have been obvious to the ordinary artisan to culture human ES cells, as taught by Thomson, in DMEM/F12 media in the presence of FGF2 and PDGF-AA on polyornithine to form neural precursors, as taught by Brustle, but growing in the precursors in a media comprising retinoic acid and growth on poly-D-lysine and laminin coated plates to induce neuronal growth, as taught by Stemple, for drug discover and/or transplantation therapies. The cited prior art provides sufficient suggestion, teaching and motivation to arrive at the claimed invention.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

The prior rejection of claims 60-63 and 87 under 35 U.S.C. 103(a) as being unpatentable over Thomson, Brustle, Stemple and Ben-Hur is maintained for reasons of record, advanced in the prior Office actions, mailed 2/23/05 and 7/29/04.

Applicants' arguments regarding Thomson, Brustle and Stemple, have been addressed above. Applicants argue that Ben-Hur does not cure the deficiencies in the art of Thomson, Brustle and Stemple because they do not teach or suggest neural progenitor cells from undifferentiated human pluripotent ES cells, namely that they teach cells obtained from neural tissue. See p. 17, last ¶ of the Response.

This is not persuasive. The claims require that the neural progenitor cells be "derived from" ES cells. Thus, although Ben-Hur do not teach cells derived from ES cells, they do teach cells that are neural progenitor cells. Thus, the conditions that Ben-Hur teach would be applicable to the claimed invention, because, as stated previously, it would be obvious for one of skill in the art to use techniques used in the differentiation of mouse ES cell art and apply these techniques to human ES cells. As stated previously, the differences between human and mouse ES cells, as recognized by the art, are in the culturing conditions to maintain the cells in an undifferentiated state. Accordingly, in view of the combined teachings, it would have been obvious for one of ordinary skill in the art, at the time of filing, to culture the human ES cells, as taught by Thomson in DMEM/F12 media in the presence of FGF and PDGF-AA, on polyornithine to form glial precursors and then, in the absence of growth factors, to form predominantly oligodendrocytes and astrocytes, as taught by Brustle, but growing the precursors on poly-D-lysine and fibronectin coated plates, in order to enhance the presence of neurons in the differentiated cells and in the presence of EGF to enhance neuron differentiation, followed by culture with EGF and T3 to produce a culture of neuronal cells, oligodendrocytes, and glia cells for drug discover and/or transplantation therapies.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

The prior rejection of claims 39-46, 64-68, 88-94 and newly added claim 97 rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson, Brustle and Ben-Hur is maintained for reasons of record, advanced in the prior Office actions, mailed 2/23/05 and 7/29/04.

Applicants present no specific argument to this rejection, other than what has been addressed above. Thus, it is maintained that, at the time of the claimed invention, it would have been obvious for one of ordinary skill in the art, to produce oligodendrocytes by culturing the human ES cells, as taught by Thomson in DMEM/F12 media, in the presence of FGF2 and EGF to form glial precursors, as taught by Brustle, and to further culture the glia cells in the presence of B27, FGF2 and EGF in combinations to provide oligodendrocytes for drug discover and/or transplantation. The cited art provides sufficient suggestion, teaching and motivation to achieve the claimed invention. The term "include" has been broadly interpreted to mean that the three growth factors, B27, FGF2 and EGF, are used in various combinations.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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